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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/775,967 | 02/02/2001 | Andrei P. Guzaev | ISIS-4682 | 9641 |

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EXAMINER

LEWIS, PATRICK T

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1623

DATE MAILED: 12/02/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/775,967

Applicant(s)

GUZAEV ET AL.

Examiner

Patrick T. Lewis

Art Unit

1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103 and 104 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103 and 104 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4, 12.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of the species wherein D^+ is protonated aromatic heterocyclic amine and E^- is tetrazolide anion in Paper No. 6 dated December 24, 2002 is acknowledged. The restriction requirement was made FINAL in Paper No. 11 dated June 11, 2003.

Applicant's Response dated September 8, 2003

2. In the Response filed September 8, 2003, claims 11-15, 36-40, 48 and 98-101 were amended, and claims 7-10, 16-20, 22-35, 41-46, 53-55, 61-65, 67-80, 86-91, 102 and 105 were canceled.

3. Applicant presented arguments directed to the rejection of claims 48-52, 56-60, 66, 81-85, 92-95, and 104 under 35 U.S.C. 112, second paragraph, and the rejection of claims 1-6, 21, 47-52, 66, 92-93, 96-97, and 104 under 35 U.S.C. 103(a). Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85 and 92-104 are pending. An action on the merits of claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85 and 92-104 is contained herein below.

4. The rejection of claims 48-52, 56-60, 66, 81-85, 92-95, and 104 under 35 U.S.C. 112, second paragraph, is maintained for the reasons of record as set forth in the Office Action dated June 11, 2003.

Art Unit: 1623

5. Applicant's arguments with respect to claims 1-6, 21, 47-52, 66, 92-93, 96-97, and 104 under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Objections/Rejections of Record Set For the in Office Action dated June 11, 2003

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 48-52, 56-60, 66, 81-85, 92-95, and 104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 48, the variable R^2 is not clearly defined. " R^2 is a 2'-substituent" does not apprise one of ordinary skill in the art of the metes and bounds of the invention. Claim 48 also recites the variables R^4 and R^5 . Variables R^4 and R^5 are not depicted in the structural formula. This ambiguity renders the claim indefinite as one of ordinary skill would not be able to determine the scope of the claimed invention.

Applicant's arguments filed September 8, 2003 have been fully considered but they are not persuasive.

Applicant argues that one of ordinary skill in the art clearly understands the meaning of the term " R^2 is a 2'-substituent". The examiner respectfully disagrees. Although it is proper to use the specification to interpret what is meant by a word or phrase in a claim, this is not to be confused with adding an extraneous limitation appearing in but not required by the specification, which is improper. The term " R^2 is a

Art Unit: 1623

2'-substituent" does not apprise one of ordinary skill in the art of the metes and bounds of the invention. The moiety represented by the variable R^2 is at the 2' position. Any moiety appearing at the 2'-position is a "2'-substituent". The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-97, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caruthers et al. Proceedings of the 2nd International Symposium on Phosphorous Chemistry Directed

Art Unit: 1623

Towards Biology (1987), pages 3-21 (Caruthers) in combination with Nurminen et al. *J. Chem. Soc., Perkin Trans. 2* (1999), pages 2551-2556 (Nurminen).

Claims 1-6, 11-15, 21, 36-40, and 47 are drawn to a method comprising reacting a nucleoside phosphoramidite with a support bound oligomer in the presence of a neutralizing agent, wherein said neutralizing agent is an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D^+E^- . Claims 48-52, 56-60, 66, 81-85, 92-95, and 104 are drawn to a method of forming an internucleoside linkage in the presence of a neutralizing agent, wherein said neutralizing agent is an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D^+E^- . Claims 96-97 are drawn to a method comprising the steps of: a) providing a solid support having a 5'-O-protected phosphorous-linked oligomer bound thereto; b) deprotecting the 5'-hydroxyl of the protected oligomer; c) optionally washing the deprotected phosphorous-linked oligomer on the solid support; d) contacting the support bound oligomer with a solution comprising a 5'-protected nucleoside phosphoramidite and a neutralizing agent; and e) oxidizing or sulfurizing the phosphite triester linkage.

Caruthers teaches the synthesis of oligonucleotides using the phosphoramidite method corresponding to the instantly claimed method. Using the procedure outlined in Table 1 (page 6), RNA was synthesized manually. Support bound nucleoside (**3a-d**) was first converted to **5a-d** by treatment with 0.3% DCA to remove the dimethoxytrityl group. After washing with dichloromethane and acetonitrile, the appropriate nucleoside phosphoramidite (**4a**, **4b**, **4c**, or **4d**) and tetrazole were added to the support.

Art Unit: 1623

Condensations were allowed to proceed for 15 minutes. Following an aqueous, hydrolytic wash the final two steps oxidation with I_2 and capping with benzoic anhydride.

Caruthers differs from the instantly claimed invention in that Caruthers does not teach the use of a neutralizing agent of D^+E^- ; however, the use of a neutralizing agent of the formula D^+E^- as a suitable replacement for tetrazole would have been obvious to one of ordinary skill in the art when the teachings of Nurminen are considered.

Nurminen teaches that ammonium azolide salts were found to be considerably more efficient catalysts than the corresponding azole acids or tertiary amine bases (Abstract, Fig. 2, Fig. 3). For instance, the relative rates obtained with *N,N*-diisopropylethylammonium tetrazolide, *N,N*-diisopropylethylamine and tetrazole were 104, 28 and 1, respectively. The salts of strong protolytes are better catalyst than those of weak ones. Other suitable tetrazole and ammonium tetrazolide salts are shown in Table 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to replace tetrazole with an ammonium azolide salt in the process taught by Caruthers as Nurminen expresses provides motivation for doing so [ammonium azolide salts were found to be considerably more efficient catalysts than the corresponding azole]. The examiner finds one of ordinary skill in the art as being a PhD in the field of nucleoside/nucleotide synthesis. Based on the teaching of Nurminen, the skilled artisan would have a reasonable expectation of success in substituting tetrazole with an ammonium azolide salt for form internucleoside linkages. The selection of a known

material based on its suitability for its intended use is well within the purview of one of ordinary skill in the art at the time of the invention and is *prima facie* obvious.

11. Claims 98-101 and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caruthers et al. Proceedings of the 2nd International Symposium on Phosphorous Chemistry Directed Towards Biology (1987), pages 3-21 (Caruthers) in combination with Nurminen et al. *J. Chem. Soc., Perkin Trans. 2* (1999), pages 2551-2556 (Nurminen).

Claims 98-101 and 103 are drawn to a composition comprising a 5'protected nucleoside phosphoramidite, a salt of formula D^+E^- , and a solid support.

Caruthers teaches support bound nucleoside (**3a-d**) which are first converted to **5a-d** by treatment with 0.3% DCA to remove the dimethoxytrityl group. After washing with dichlormethane and acetonitrile, the appropriate nucleoside phosphoramidite (**4a**, **4b**, **4c**, or **4d**) and tetrazole [neutralizing agent] were added to the support.

Caruthers differs from the instantly claimed invention in that Caruthers does not teach the use of a neutralizing agent of formula D^+E^- ; however, the use of a neutralizing agent of the formula D^+E^- as a suitable replacement for tetrazole would have been obvious to one of ordinary skill in the art when the teachings of Nurminen are considered.

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Art Unit: 1623

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It would have been obvious to one of ordinary skill in the art at the time of the invention to replace tetrazole with an ammonium azolide salt in the composition taught by Caruthers as Nurminen expresses provides motivation for doing so [ammonim azolide salts were found to be considerably more efficient catalysts than the corresponding azole]. The examiner finds one of ordinary skill in the art as being a PhD in the field of nucleoside/nucleotide synthesis. Based on the teaching of Nurminen, the skilled artisan would have a reasonable expectation of success in substituting tetrazole with an ammonium azolide salt for form internucleoside linkages. The selection of a known material based on its suitability for its intended use is well within the purview of one of ordinary skill in the art at the time of the invention and is *prima facie* obvious.

Conclusion

12. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, and 103-104 are pending. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, and 103-104 are rejected. No claims are allowed.


Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD
Examiner
Art Unit 1623



James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

ptl
November 24, 2003